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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KAM, CHIH MIN	
ART UNIT	PAPER NUMBER
1656	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/926,391	SHIOJIRI ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3 and 20-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-41* is/are rejected.

7)☒ Claim(s) *3 and 20-23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/7/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 3 and 20-41 are pending.

Applicants' amendment filed November 7, 2006 is acknowledged. Applicant's response has been fully considered. Claims 24, 25, 30-32, 34-36, 39 and 40 have been amended, and claims 1 and 4-19 have been cancelled. Therefore, claims 3 and 20-41 are examined.

Priority

2. An English translation of the priority document, Japan Application No. 11/118633, filed November 7, 2006 is acknowledged. Therefore, the priority date of the instant application is 4/26/1999.

Withdrawn Claim Rejections - 35 USC § 112

3. The previous rejection of claims 1, 4-19 and 24-41, under 35 U.S.C. 112, first paragraph, written description, is withdrawn in view of applicants' amendment to the claim, applicants' cancellation of the claims, and applicants' response at pages 14-19 in the amendment filed November 7, 2006.

4. The previous rejection of claims 8-10, 12-14 and 16-18, under 35 U.S.C. 112, first paragraph, scope of enablement, is withdrawn in view of applicants' cancellation of the claims in the amendment filed November 7, 2006.

5. The previous rejection of claims 1, 4-19 and 24-41, under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicants' amendment to the claim, applicants' cancellation of the claims, and applicants' response at page 22 in the amendment filed November 7, 2006.

Withdrawn Claim Rejections - 35 USC § 102

6. The previous rejection of claims 24 and 25 under 35 U.S.C. 102(a) as anticipated by Stewart et al. (WO 00/11022, published on March 2, 2000), is withdrawn in view of applicants' amendment to the claim, and applicants' response at pages 21-22 in the amendment filed November 7, 2006.

Claim Objection

7. Claim 24 is objected to because of the use of the term "m represents an integer of 0 or 1". Since the claim only recites when m is 1, not when m is 0, the term should be deleted.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 24-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound of formula (1) having a naphthyl group, a melanocyte-stimulating hormone inhibitory composition or a cosmetic or external preparation for the skin comprising the compound of formula (1), wherein Ar is an unsubstituted naphthyl group, R^4 is an unsubstituted basic amino acid side chain, and R^7 is the side chain of a neutral amino acid having a hydrophobic side chain; and a method of suppressing pigmentation of skin in a mammal by topically administering to the mammal the compound of formula (1) having a naphthyl group, wherein Ar is an unsubstituted naphthyl group, R^4 is an unsubstituted basic amino acid side chain, and R^7 is the side chain of a neutral amino acid having a hydrophobic side chain, does not reasonably provide enablement for all the compounds of formula (1), a melanocyte-stimulating hormone inhibitory composition, a cosmetic or external preparation for the skin, or a whitening

agent comprising the compound of formula (1); and a method of whitening, regulating immunofunction or regulating appetite in a subject by administering an agent comprising any compound of Formula (1). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 24-41 encompass a compound of formula (1) having a naphthyl group (claims 24, 25), a melanocyte-stimulating hormone inhibitory composition (claims 26-29) or a cosmetic or external preparation for the skin (claims 33, 37, 41) or a whitening agent (claim 38) comprising the compound of formula (1), and a method of whitening (claims 30, 34), regulating immunofunction (claim 31, 35, 39) or regulating appetite (claims 32, 36, 40) in a subject by administering an agent comprising the compound of Formula (1). The specification, however, only discloses cursory conclusions without data supporting the findings, which state that the present invention provides di- or tri-peptide derivatives with the Formula (1) having a naphthyl group, which can inhibit the action of melanocyte-stimulating hormone, thereby the compound can be used as an active ingredient in a melanocyte-stimulating hormone inhibitory composition, a whitening agent, an immunofunction controlling agent, an appetite controlling agent, or a cosmetic preparation (pages 3-6). There are no indicia that the present application enables the full scope in view of a compound of Formula (1) and a method of whitening, regulating immunofunction or regulating appetite in a subject by administering an agent comprising the compound of Formula (1) as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in

In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the absence or presence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding various compounds of Formula (I), e.g., undefined substituent on the naphthyl group, R^4 is hydrogen, and R^7 is hydrogen (including Nal-Gly-GlyNH_2), and their effects in whitening, regulating immunofunction or regulating appetite in a subject, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

The specification merely discloses specific compounds of Formula (1) such as D-1-Nal-Arg-LeuNH_2, D-2-Nal-Arg-LeuNH_2, L-1-Nal-Arg-LeuNH_2, and L-2-Nal-Arg-LeuNH_2 have inhibitory activity against MSH (test Example 1), suppress the melanin formation (text Example 2), and suppress pigmentation in brown guinea pig model (test Example 4), there are no working examples indicating the use of compounds of Formula (1) in regulating immunofunction or regulating appetite in a subject for in vivo treatment.

(3). The state of the prior art and relative skill of those in the art:

The related art (e.g., references shown in pages 2-3 of the specification) indicates the use of MSH inhibitors have a pigmentation inhibitory activity. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to

provide teachings on the identities of various compounds of formula (1) that are effective in whitening, regulating immunofunction or regulating appetite in a subject to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass a compound of formula (1) having a naphthyl group and a method of whitening, regulating immunofunction or regulating appetite in a subject by administering an agent comprising the compound of Formula (1), however, the identities of active compounds of Formula (1) and their in vivo effects are not adequately described in the specification, the invention is unpredictable regarding the structures of the compounds of Formula (1) that are effective in the treatment.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a compound of formula (1) having a naphthyl group and a method of whitening, regulating immunofunction or regulating appetite in a subject by administering an agent comprising the compound of Formula (1). While the specification discloses specific compounds of Formula (1) such as D-1-Nal-Arg-LeuNH_2, D-2-Nal-Arg-LeuNH_2, L-1-Nal-Arg-LeuNH_2, and L-2-Nal-Arg-LeuNH_2 have inhibitory activity against MSH (test Example 1), suppress the melanin formation (text Example 2), and suppress pigmentation in brown guinea pig model (test Example 4), the specification does not describe the use of various compounds of Formula (1) in whitening, regulating immunofunction or regulating appetite in a subject, nor demonstrates how to extrapolate the in vitro effect to in vivo treatment. Furthermore, there are no working examples indicating the compounds of Formula (1) with

different substituents on naphthtyl group, hydrogen as R^4, and hydrogen as R^7 (e.g., Nal-Gly-GlyNH_2) have inhibitory activity against MSH and the use of compounds of Formula (1) in regulating immunofunction or regulating appetite either in vitro or in vivo treatment. Since the specification does not provide sufficient teachings on the use of various compounds of Formula (1) that are effective in whitening, regulating immunofunction or regulating appetite in a subject, it is necessary to have additional guidance and to carry out undue experimentation to identify the compounds of Formula (1) that are effective for in vivo treatment.

(6). Nature of the Invention

The scope of the claims encompasses a compound of formula (1) having a naphthyl group and a method of whitening, regulating immunofunction or regulating appetite in a subject by administering an agent comprising the compound of Formula (1), but the specification does not provide sufficient teachings on the identities of active compound of Formula (1) and their effects either in vitro or in vivo treatment. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broader than the enabling disclosure. The working examples do not demonstrate the claimed compounds and methods associated with the variants, the effects of the compound of Formula (1) are unpredictable, and the teachings in the specification are limited, therefore, it is necessary to carry out undue experimentation to identify the compounds of Formula (1) that are active in the treatment.

Response to Arguments

Applicants indicate the Examiner has rejected the method of treatment claims (i.e., methods of whitening, regulating immunofunction, and regulating appetite) as lacking

enablement, and the primary criticism is that the specification merely discloses the tested compounds have inhibitory activity against melanocyte-stimulating hormone (MSH), but does not exemplify the effectiveness of these tested compounds with respect to the various claimed methods. Applicants have amended the claims to limit the inventive compounds to tripeptides (i.e., m=l), and discussed several references correlating the demonstrated MSH inhibitory activity of the claimed compounds with efficacy in the various cited methods on pages 1-3 of the specification and submit four references (in IDS filed 11/7/06) that establish that there is an art known correlation between MSH inhibition and efficacy in the various claimed methods. Applicants submit that they are the first to find the activities in the basic combination of a naphthyl group with a basic amino acid and neutral amino acid (Nal-(basic amino acid)-(neutral amino acid)). Those skilled in the art would easily be able to modify such a combination based on the description in the present specification without undue experimentation. Further, with the established link between MSH inhibitory activity and the various pharmacological activities presently claimed, Applicants submit that the full scope of the presently claimed invention is sufficiently enabled as required by 35 U.S.C. § 112, first paragraph (pages 19-21 of the response).

Applicant's response has been fully considered, however, the arguments are not found persuasive because of the following reasons. While the amended claim 24 is directed to a tripeptide having a naphthyl group, the compounds of formula (1) also include a tripeptide with an undefined substituent on the naphthyl group, R^4 being hydrogen, and R^7 being hydrogen, e.g., Nal-Gly-GlyNH_2, which does not fit in the structure of Nal-(basic amino acid)-(neutral amino acid) and its MSH inhibitory activity is not known. Thus, it appears not all of compounds of

formula (1) can be predicted to have MSH inhibitory activity. Regarding using the compound of formula (1) in the claimed method of whitening, regulating immunofunction or regulating appetite, although the correlation between MSH inhibition and efficacy in the various claimed methods in known in the art, the compounds used in the art are structurally different from the claimed compound of formula (1), and it is known that the efficacy of the tested compound for in vivo treatment is dependent on its structure, inhibitory potency and in vivo stability. Since the specification does not provide sufficient teachings on the in vivo treatment or how to extrapolate the in vitro effect to in vivo treatment, it requires undue experimentation to identify the compounds of formula (1) that are effective in the claimed methods. Thus, the full scope of the claims is not enabled.

New Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 24-26, 38 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Janecka *et al.* (J. Med. Chem. 38, 2922-2924 (1995)).

Janecka *et al* teach a series of reduced analogs of LHRH such as compound 29, AcDNal-Arg-DAlaNH$_2$, which meet the structural criteria of the peptide of formula (1), for example, AcDNal-Arg-DAlaNH$_2$ corresponds to the tripeptide of formula (1), where Ar is 2-naphthyl, n is 1, X^1 is CH_2, R^1, R^2 and R^3 are each H, R^6 is CH_3CO-NH, R^4 is arginine side chain, X^2 is single bond, X^3 is NH, m is 1, R^7 is CH_3 group, R^8 is H (or, R^7 is H, R^8 is CH_3 group), X^4 is NH, and R^9 is H (Table 1, compound 29; claims 24 and 25). Compound 29 can be prepared with a

pharmaceutically acceptable carrier such as HEPES buffer (page 2924, right column), which meet the criteria of claims 26, 38 and 41, because the compound contains the same structure as the claimed peptide of formula (I), thus it would be expected to have melanocyte-stimulating hormone inhibitory activity. Furthermore, the claim merely recites a whitening agent or a cosmetic preparation comprising the peptide of formula (I) as an active ingredient, and the compound 29 is an active ingredient in a composition for *in vitro* testing, therefore, claims 26, 38 and 41 are anticipated by the reference.

Claim Objections

10. Claims 3 and 20-23 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

11. Claims 24-41 are rejected, and claims 3 and 20-23 are objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Primary Patent Examiner

CHIH-MIN KAM
PRIMARY EXAMINER

CMK
January 16, 2007